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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 9577-32 LAB	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA 02/01360	International filing date *(day/month/year)* 05.09.2002	Priority date *(day/month/year)* 07.09.2001
International Patent Classification (IPC) or both national classification and IPC A61K9/22		
Applicant INTELLIPHARMACEUTICS CORP.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.03.2003	02.02.2004
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baumgärtner, H Telephone No. +49 89 2399-8480

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA 02/01360

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-25 received on 08.01.2004 with letter of 06.01.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1, 3, 4, 8, 11, 13, 16, 17, 18, 24

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1, 3, 4, 8, 11; 13, 16; 17, 18, 24 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10, 13-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	11, 12, 24
Industrial applicability (IA)	Yes:	Claims	1-24 (in part)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated January 6th, 2004 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

claim 1 "**plurality** of **discrete** vehicles" and claim 23 "more than one **discrete** vehicle"

A basis for these amendements has not been given. The possible references thereto in the description, cf. p.1/l.30 and p.2/l.1 "population of ...", cf. p.3/l.9 "one or more different vehicles...", however, are not considered to represent an admissible basis.

Thus, the report will be based on claims 1-24 as previously on file.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Incomplete Search 1, 3, 4, 8, 11, 13, 16, 17, 18, 24

Present claims 1, 3, 4, 8, 11, 13, 16, 17, 18, 24 relate to an extremely large number of possible compounds/pharmaceutical formulations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/pharmaceutical formulations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope has been impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/pharmaceutical formulation:

vehicles (claims 1/24), cf. claim 2
active agents (claims 1/13/16/17/18/24), cf. claims 14 and 15
amino acid (claims 1/3/4/24) cf. description examples
buffer (claims 1/24), cf. claim 5
polymer (claims 1/24) cf. claim 6
housing (claims 1/24) cf. claim 7

The definition of the vehicle shapes (claim 8) and of the general terms as "cryoprotectant, lyoprotectant and surfactant" (claim 11) are not precise enough and do not render it possible to cover the whole range of the included meaning.

The same holds true for claims 19-23 referring to release order kinetics. It goes without saying that the definition of technical features by parameters does not provide a mean to clearly compare the claimed subject-matter vis-à-vis the prior art, thus rendering it impossible to carry out a complete search which would include any of the existing prior art having the same - implicit - features.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

subject-matter

Claim 1 **controlled release delivery device** comprising
more than 1 vehicle compr. up to 60% b.w. **active agent**
up to 60% b.w. **amino acid**
up to 60% b.w. **buffer**
up to 70% b.w. polymer
wherein said **vehicle** is provided **within a housing**

Claim 24 s. claim 1 (plus)
1 or more agents selected from [...] cryoprotectant, lyoprotectant, surfactant, activated charcoal and super activated charcoal
wherein said vehicle is provided within a housing made [...] from [...] **gelatin, hydroxypropyl methyl cellulose, non-toxic metal or metal alloy and non-toxic plastic**

The documents which are referred to in this communication are numbered in the order of their listing in the International Search Report.

D1 US4940588 [X]
Controlled release powder containing **discrete micro-articles** for use in edible,

pharmaceutical etc. sustained release compositions (col.2/l.60-63).
The particle comprise an **active ingredient** (cf. col.4/l.10-col.8/l.42) optionally an excipient in intimate admixture with at least one **non-toxic polymer** (col.2/l.65-66 and col.3/l.23- col.4/l.6). **The excipient may also be an active transport agent such as e.g. one or more amino acids** (col.7/l.32-34). The excipient may comprise basic material e.g. **sodium citrate** (col.7/l.43).
The particles may also be **loaded into capsules** (col.7/l.58-60).

D2 EP0960620 [X]
The composition is in the form of a simple powder blend or granules of the active ingredient and the carrier, together with any optionally included excipients, filled into an enteric capsule, i.e., a capsule which is coated with an enteric polymer or which is made from an enteric polymer [0011]/page 3.
On page 2/[0004] Japanese Patent 05-194,225 discloses tablets, granules and capsule formulations where the benzimidazole gastric ulcer inhibitors are **stabilized by** compounding with **amino acids and buffering agents**.

D3 US5840329 [X]
A **pulsatile drug delivery system** for the release of an active medicament in pulsed dosages when exposed to an aqueous environment which comprises one or more groups of particles which contain the active medicament, **enclosed in a solid dosage form (formulated into tablets or capsules cf. claim 7)** with each of said groups having a distinct pattern of drug release based upon its combination of controlled release layers, swelling layers, and coating layers (claim 1).
Plasticizers (eg. triethyl citrate) are preferably included in the matrix material to optimize the diffusion of active medicament through the controlled-release layer for a desired release pattern (col.7/l.58-65)

When applicable, pharmacologically inert cationic compounds can be included in the controlled release layer, or are coated onto the sugar/starch or cellulose seed with pharmaceutical binders prior to the coating of the controlled release layer, so as to modify the rate of drug release. **Such cationic compounds include, but are not limited to, lysine and arginine** (col.8/l.5-11).

D4 WO9011070 [X]
A controlled release delivery device for delivering macromolecular proteins comprising an inner

compartment which contains a **plurality of non-uniform beadlets** (= a pellet, tablet or microcapsule claim 9), said beadlets comprising a rupturable wax shell which completely surrounds a core matrix containing the macromolecular protein; and a **water-soluble outer capsule** completely surrounding said inner compartment (claim 1). In example 8/p.17 L-Arginine is one of the ingredients. (For **buffering** cf. p.6/l. 31).

D5 WO9428882 [Y]
for **housing - pellets** with various films etc.
Refers to a multiparticulate pulsatile drug system comprising at least two different populations of polymer coated pellets.
The coating on the pellets of each population being sufficiently different from the coating on the pellets of every other population in the unit dose (p.2/last para - p3./1st full para).

D6 US6228400 [Y]
granules of omeprazole which contains (a) an **inert core** made of **starch or the like**
(b) a **drug emulsion,** comprising the drug, a **non-inionic surfactant**, a **basic amino acid** (the most preferably basic amino acid being **arginine,** cf. col.4/l.34) and water
(c) a **protective coating (plasticizer** used in the enteric coating **includes triethyl citrate** etc. cf. col.4/l.40-42).

D7 US5972389 [Y]
Drug (cf. col.5/l.64-col.6/l.24) dosage form **comprising a plurality of solid particles** or **pellets** of a solid-state drug **dispersed within a polymer** (col.1/l.67-col.2/l.2), protective vesicle respectively (col.6/l.32). Suitable **vesicles are i.a. microspheres composed of amino acids** (col.6/l.34-35).

Novelty (i), Inventive Step (ii) und Industrial Applicability (iii) - Art. 33 (1)-(4)
i.
The subject-matter of the claims 1-8 in **not novel** in the light of
D1 US4940588
D2 EP0960620
D3 US5840329

The subject-matter of claims 9-10 (= size of granules etc.) and 11 (i.a. surfactant) is (implicitly)

anticipated by the mentioned prior art documents.
The addition of active agents as claimed in claims 13-18 is not novel (cf. e.g. D1/col.4/l.10 seq., D2/col.12/l.29 seq. and D4/p.12/l.31).
Claims 19-23 delimiting the subject-matter by way of the release kinetics are at present again considered to have been implicitly disclosed by the prior art.

ii.

It should be noted that the claims do not appear to fulfil the requirements of inventive step.
Even if the subject-matter of claim 11 and 12 has nowhere been explicitly disclosed, the addition of those particular agents forms part of the routine procedures in the preparation of the respective pharmaceutical formulations.
By analogy this assessment is to be applied to claim 24 as well.

1. A controlled release delivery device comprising;

- a plurality of discrete vehicles provided within a housing, wherein each of said vehicles are provided as separate granules, beads, pellets or tablets and mixtures thereof, and each of said vehicles comprises up to 60% by wgt active agent; up to 60% by wgt amino acid, up to 60% by wgt buffer, and up to 70% by wgt polymer.

2. The device of claim 1, wherein said amino acid is selected from the group consisting of nonpolar, polar neutral, polar basic and polar/acid amino acids.

3. The device of claim 1, wherein the buffer is selected from the group consisting of organic and inorganic buffers.

4. The device of claim 4, wherein said buffer is selected from the group consisting of phosphate, citrate, HEPES, succinate, histidine, maleate, lactate, and acetate buffers and mixtures thereof.

5. The device of claim 1, wherein said polymer is selected from the group consisting of cellulose esters, cellulose ethers, polyethylene oxide, carbomer, cyclodextrins, polyethelene glycol, dextran, polyvinylpyrrolidone, lactide/glycolide copolymers, poly(ortho esters), polyanhydrides, polyvinyl alcohol, alginates, polysaccharides, polyamides, polyvinyl chloride, polyethylene vinyl acetate, polvinyl pyrrolidone, polyurethanes, hydrogels, silicone polymers, polyacrylates, polymethacrylates, polyanhydrides, poly amino carbonates, deacetylated chitin, collagen, polyisobutylenes, gelucire, glyceryl behenate and mixtures thereof.

6. The device of claim 1, wherein said housing is made of a material selected from the group consisting of gelatin, hydroxypropyl methyl cellulose, a non-toxic metal, or metal alloy and a non-toxic plastic or a combination thereof.

7. The device of claim 1, wherein said granules, pellets, beads or tablets may be regular or irregular in shape.

8. The device of claim 1, wherein said granules, pellets, beads or tablets have a diameter and thickness of less than about 40 mm.

AMENDED SHEET

9. The device of claim 8, wherein said granules, pellets, beads or tablets have a diameter and thickness of less than about 13 mm.

10. The device of claim 1, wherein said vehicles additionally comprises an agent selected from the group consisting of cryoprotectant, lyoprotectant and surfactant.

11. The device of claim 1, wherein said vehicles additionally comprises activated or super activated charcoal.

12. The device of claim 1, wherein said active agent is selected from the group consisting of a pharmaceutical active, protein, peptide, algicide, fungicide, germicide, herbicide, insecticide, pesticide and mixtures thereof.

13. The device of claim 13, wherein said active agent is selected from the group consisting of Acetaminophen/Codeine, Albuterol, Alendronate, Allopurinol, Alprazolam, Amitriptyline, Amlodipine, Amlodipine/Benazepril, Amoxicillin, Amoxicillin/Clavulanate, Amphetamine Mixed Calsts, acarbose, Atelolol, Atorvastatin, Azithromycin, Beclomethasone, Benazepril, Bisoprolol/HCTZ, Brimonidine, Calcitonin Salmon, Carbamazepine, Carisoprodol, Carvedilol, cefprozil, Cefuroxime, Clecoxib, Cephalexin, Cetirizine, Ciprofloxacin, Cisapride, Citalopram, Clarithromycin, Clonazepam, Clonidine, Clopidogrel, Clotrimazole/Betamethasone, Cyclobenzaprine, Diazepam, Misoprostol, Digoxin, Divalproex, Donepezil, Doxazosin, Enalapril, Erythromycin, Estradiol, Ethinyl Estradiol/Norethindrone, Famotidine, Felodipine, Fexofenadine, Fexofenadine/Pseudoephedrine, Fluoxetine, Fluticasone Propionate, Fluvastatin, Fluvoxamine maleate, Fosinopril, Furosemide, Gemfibrozil, Glimepiride, Glyburide, Guaifenesin/Phenylpropanolamine, Granisetron HCl, Hydrochlorothiazide, Hydrocodone w/APAP, Ibuprofen, Ipratropium, Ipratropium/Albuterol, Irbesartan, Isosorbide Mononitrate, Lansoprazole, Latanoprost, Levofloxacin, Levonorgestrel/Ethinyl Estradiol, Levothyroxine, Lisinopril, Lisinopril/HCTZ, Loratadine, Loratidine/Pseudoephedrine,Lorazepam, Losartan, Losartan/HCTZ, Lovastatin, Methylprednisolone, Methylphenidate, Metoprolol, miglitol Mometasone, Montelukast, Mupirocin, Naproxen, Nitrofurantoin, Nizatidine, Olanzapine, Oxaprozin, Oxycodone, Oxycodone/APAP, Paroxetine, Penicillin VK, Phenytoin, Potassium, Chloride, Pramipexole HCl, Pravastatin, Predinisone, Promethazine, Propoxyphene N/APAP, Propranolol, Quinapril, Raloxifene, Ramipril, Ranitidine, repaglinide, Risperidone, Rofecoxib, Salmeterol, Sertraline, Sildenafil Citrate, Simvastatin, Sumatriptan, Tamoxifen, Tamsulosin,

Tamazepam, Terazosin, Terbinafine, Tobramycin/Dexamethasone, Tolterodine, Tranylcypromine sulfte, Trazodone, Triamterene/HCTZ, Troglitazone, Valsartin, Venlafaxin, Warfarin, Zafirlukast and Zolpidem.

14. The device of claim 13, wherein said active agent is one to treat HIV or AIDS and is selected from the group consisting of Abacavir, amprenavir, stavudine, zalcitabine, didanosine, delavirdine, efavirenz Hydroxyurea, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir Saquinavir, stavudine and zidovudine.

15. The device of claim 13, wherein said pharmaceutical active is selected from the group consisting of hormones and prostaglandins.

16. The device of claim 13, wherein said pharmaceutical active is an anticancer agent.

17. The device of claim 13, wherein said active agent is an active or inactive metabolite or salt thereof, of a pharmaceutical agent.

18. The device of claim 13, wherein two or more vehicles are provided wherein at least one vehicle provides a zero order release and at least one vehicle provides a first order release of pharmaceutically active substance.

19. The device of claim 13, wherein at least one vehicle provides a zero order release of pharmaceutically active substance.

20. The device of claim 13, wherein at least one vehicle provides a first order release of pharmaceutically active substance.

21. The device of claim 13, wherein at least one vehicle provides a pseudo first order release of pharmaceutically active substance.

22. The device of claim 13, wherein said device provides for the controlled release delivery of more than one pharmaceutically active substance that are incompatible.

23. A controlled release delivery device comprising:

- more than one discrete vehicle provided within a housing, each vehicle being provided as separate granules, beads, pellets or tablets and mixtures thereof, each vehicle comprising up to 60% by wgt active agent, up to 60% by wgt amino acid, up to 60% by weight buffer, up to 70% by wgt polymer, and one or more agents selected from the group consisting of cryoprotectant, lyoprotectant, surfactant, activated charcoal and super activated charcoal;

wherein said more than one discrete vehicle is provided within a housing comprising a material selected from the group consisting of gelatin, hydroxypropyl methyl cellulose, non-toxic metal or metal alloy and non-toxic plastic.

24. The device of claim 1 or 24, wherein said polymer is different in each of said vehicles.

25. The device of claim 1 or 24, wherein said active agent is different in each of said vehicles.